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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,693	12/05/2001	Ajay Bhatia	210121.515C2	1153

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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	10/007,693	BHATIA ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/25/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The amendment filed on 7/25/03 has been entered into the record. Claims 1-9 and 13-18 have been canceled. Claims 11, 19 and 20 have been amended. Claims 11, 19 and 20 are pending in the application.

Rejections Withdrawn

2. In view of amendment to the claims and arguments of record, the rejection under 35 U.S.C. 112, Second paragraph is withdrawn.

3. In view of amendment to the claim 19, the rejection under 35 U.S.C. 112, first paragraph is withdrawn.

Rejections Maintained

4. The rejection of claim 20 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulant and a second component consisting of a polypeptide as set forth in SEQ.ID.NO: 139 does not reasonably provide enablement for a composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulant and a second component consisting of a polypeptide having at least 95 % and 99% identity with the polypeptide sequence of SEQ.ID.NO: 139 is maintained as set forth in the previous office action.

With regard to %identity, the specification is not enabled for polypeptide which has at least 95 % and 99% amino acid sequence identity with SEQ.ID.NO: 139 because it is unclear to one skilled in the art what sequences are embraced by the claim. If it is unclear to one skilled in the art what sequences are embraced by a claim which is based on a specification to determine percent identity, the specification is non-enabling, since one skilled in the art would not be able to make and use those sequences without undue experimentation.

Applicant has not set forth which amino acid (s) in the polypeptide SEQ.ID.NO 139 can be deleted or inserted or substituted to give rise to the polypeptide having at least 95 % and 99% identity with SEQ.ID.NO: 139. After these alterations or modifications whether the polypeptide can still retain the activity of stimulating T-cells is not set forth in the specification.

The specification provides guidance and direction with regard to an isolated polypeptide comprising 660 amino acids as set forth in the SEQ.ID.NO 139, which is designated as CT 622.

However, the specification fails to teach a polypeptide comprising at least 95 % and 99% identity to SEQ.ID.NO 139 and it's use in a method for stimulating and/or expanding T-cells. It is well known that for proteins, for example, even a single amino acid change can destroy the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Applicant failed to give direction to what modification have been done to SEQ.ID.NO 139 to give rise to at least 95 % and 99% sequence identity to SEQ.ID.NO 139 and what changes would have an adverse effect on the function of this peptide is not predictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 139 can be varied and still achieve a protein that is functional in stimulating and/or expanding T-cells specific for Chlamydia protein. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Applicants' arguments filed on 7/25/03 have been fully considered but they are not deemed to be persuasive.

Applicant asserts that the full length Chlamydia protein, CT 875 having the amino acid sequence SEQ.ID.NO: 139 reacts specifically with human $CD4^+$ T-cells and one pool containing the clone E5 -A8- 85 (SEQ.ID.NO: 34) encoding a large region of polypeptide of CT 875 protein. Further, applicant states that CT875 is immunogenic and is reactive in 8/11 human T cell lines tested.

The examiner clearly indicated that the applicant is enabled for a composition and a method of stimulating and /or expanding T-cells specific for Chlamydia comprising the amino acid sequence, SEQ.ID.NO: 139 and not enabled for a composition and a method of stimulating and /or expanding T-cells specific for Chlamydia having at least 95% and 99% sequence identity with the peptide of SEQ.ID.NO 139. Besides, it is the position of the examiner that the full-length Chlamydia protein having the amino acid sequence, SEQ.ID.NO: 139 is represented by CT622 = 660aa and not by CT875 = 598 aa (please see amendment 2/12/03, Paper # 10) as applicant stated in the response. Therefore, the arguments regarding CT875 protein and the clone E5 -A8- 85 (SEQ.ID.NO: 34 =1433 bp is a hypothetical gene encoding hypothetical protein CT875) are not correct. Applicant's arguments based on clone, E5 -A8- 85 (SEQ.ID.NO: 34) is not relevant since the referred hypothetical gene encoding hypothetical peptide is not same as the claimed polypeptide with 95% and 99% identity to SEQ.ID.NO: 139. The examiner understands the complexity of the subject matter and reviewed the application and found no clone that contains a polypeptide with 95% and 99% identity to SEQ.ID.NO: 139.

As examiner pointed out and explained above making and expanding specific T-cell clones using antigen presenting cell that expresses or pulsed with immunogenic portion of a polypeptide, SEQ.ID.NO: 139 is unpredictable because the instant specification provides absolutely no guidance as to which amino acid residues in SEQ ID NO: 139 of the instant application are essential for the functional and structural integrity of T-cells, specific for Chlamydia. The specification fails to teach modifications made to the polypeptide SEQ.ID.NO: 139. However, the art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein as explained in the rejections. In addition, substitution of a single amino acid residue in a critical TCR region changes TCR-mediated signal transduction, membrane localization and function in T-

lymphocytes (see figures and abstract of Yasuda et al 2000, Journal of Immunology 165; 3226-3231). In conclusion, the instant specification provides no guidance that would permit an artisan to practice the invention commensurate with the scope of the instant claim.

New Rejections Based on Amendment

Claim Rejections - 35 USC 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 19 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for stimulating and /or expanding T cells specific for Chlamydia CT622 protein having the amino acid sequence set forth in SEQ.ID.NO: 139, comprising contacting T cells with an antigen presenting cell expressing or pulsed with the polypeptide, SEQ.ID.NO: 139 does not reasonably provide enablement for a method for stimulating and /or expanding T cells specific for Chlamydia CT622 protein comprising contacting T cells with an antigen presenting cell expressing or pulsed with at least an immunogenic portion of a polypeptide selected from the group consisting of a polypeptide having at least 95 % and 99% identity with the polypeptide sequence of SEQ.ID.NO: 139.

The specification is not enabled for a polypeptide which has at least 95 % and 99% identity to SEQ.ID.NO: 139 because it is unclear to one skilled in the art what sequences are embraced by the claim. If it is unclear to one skilled in the art what sequences are embraced by a claim which is based on a specification to determine percent identity, the specification is non-

enabling, since one skilled in the art would not be able to make and use those sequences without undue experimentation.

Applicant has not set forth which amino acid (s) in the polypeptide SEQ.ID.NO 139 can be deleted or inserted or substituted to give rise to the polypeptide having at least 95 % and 99% identity with SEQ.ID.NO: 139. After these alterations or modifications whether the polypeptide can still retain the activity of stimulating T-cells is not set forth in the specification.

The specification provides guidance and direction with regard to an isolated polypeptide comprising **660** amino acids as set forth in the SEQ.ID.NO 139, which is designated as CT 622 reacts with human $CD4^+$ T-cells. The specification also teaches by screening an expression library of *C.trachomatis* serovar E, CT622 positive T-cell pools have been identified and recombinant CT622 is reactive in 3/11 human T-cell lines tested. However, the specification fails to teach immunogenic portions of a polypeptide comprising at least 95 % and 99% amino acid sequence identity to SEQ.ID.NO 139 and it's use in a method for stimulating and/or expanding T-cells. It is well known that for proteins, for example, even a single amino acid change can destroy the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Applicant failed to give direction to what modification have been done to SEQ.ID.NO 139 to give rise to 95 % and 99% sequence identity to SEQ.ID.NO 139 and what changes would have an adverse effect on the function of this peptide is not predictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable

changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 139 can be varied and still achieve a protein that is functional in stimulating and/or expanding T-cells specific for Chlamydia protein.

The induction and expansion of specific T-cells to peptide epitopes (i.e., immunogenic portions) from protein antigens is highly complex as taught by the prior art, Unanue. ER 1999 (see attached review article, American Journal of Pathology; 154; 651-664). It is apparent that the immunogenicity of T-cell epitopes has been particularly difficult to define because of the added complexity resulting from the need for a first step for processing, and peptide interaction with major histocompatibility molecules (MHC) proteins. Following a period of internalization by the macrophages, the T-cells were able to recognize products of bacteria, Listeria

monocytogenes. However, chemical neutralization of proteolytic activity abolished the expansion of the T-cell epitopes (see page 652, left column, first paragraph). Thus interaction of T-cells and APC appear to be complex with peptides. Further, In view of the complex nature of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

Claim Rejections - 35 USC 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 19 and 11 are rejected under 35 U.S.C. 112, Second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 11 are rejected as being vague for the recitation of "CT875 protein" because it appears from the specification that "CT622" protein containing 660 amino acids is the sequence set forth in SEQ.ID.NO: 139.

Status of Claims

9. No claims are allowed.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP ' 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

10/16/03

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600